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A time series analysis of the relationship between apparent temperature, air pollutants and ischemic stroke in Madrid, Spain

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ABSTRACT

The understanding of the role of environment on the pathogenesis of stroke is gaining importance in the context of climate change. This study analyzes the temporal pattern of ischemic stroke (IS) in Madrid, Spain, during a 13-year period (2001–2013), and the relationship between ischemic stroke (admissions and deaths) incidence and environmental factors on a daily scale by using a quasi-Poisson regression model. To assess potential delayed and non-linear effects of air pollutants and Apparent Temperature (AT), a biometeorological index which represents human thermal comfort on IS, a lag non-linear model was fitted in a generalized additive model.

The mortality rate followed a downward trend over the studied period, however admission rates progressively increased. Our results show that both increases and decreases in AT had a marked relationship with IS deaths, while hospital admissions were only associated with low AT. When analyzing the cumulative effects (for lag 0–14 days), with an AT of 1.7 °C (percentile 5%) a RR of 1.20 (95% CI, 1.05–1.37) for IS mortality and a RR of 1.09 (95% CI, 0.91–1.29) for morbidity is estimated. Concerning gender differences, men show higher risks of mortality in low temperatures and women in high temperatures. No significant relationship was found between air pollutant concentrations and IS morbi-mortality, but this result must be interpreted with caution, since there are strong spatial fluctuations of the former between nearby geographical areas that make it difficult to perform correlation analyses.

1. Introduction

Stroke is a major global health issue and, particularly, it is the second cause of death for people above the age of 60 in developed countries and the most frequent cause of disability in adults.

According to Global Burden of Disease Study estimates of stroke incidence for the years 1990 and 2016, the lifetime risk of stroke was 24.9% globally. Among the 21 GBD regions, the highest risk was estimated in East Asia (38.8% [37.0–40.6]), while Eastern Sub- Saharan Africa (11.8% [95% UI: 10.9–12.8]) had the lowest risk (Feigin et al., 2018).

About 85% of all strokes are due to ischemia, and in the majority of ischemic stroke events, the mechanism responsible is understood (Silva et al., 2011).

Global epidemiology of stroke is changing. Standardized rates of stroke mortality by age have decreased in the past 2 decades while the absolute numbers of people who suffer a stroke every year are increasing (Feigin et al., 2015).

In the context of climate change, some authors have analyzed the association of different atmospheric variables (e.g., average temperature, precipitation, barometric pressure or relative humidity) and stroke incidence. However, these studies often report divergent results (Guan et al., 2018).

For example, in 2018, Chu et al. analyzed the relationship between weather variables and stroke outcomes in the United States, concluding that the increases in temperature and precipitation were associated with lower odds of mortality (OR 0.95, CI 0.93–0.97, $P < 0.0001$ and OR 0.95, CI 0.90–1.00, $P = 0.035$, respectively) (Chu et al., 2018).

However, Tian et al. in China, when studying the effects of temperature variability on cardiovascular disease, found that the increase

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in the air temperature was associated with significant growths of ischemic stroke hospital admissions (Tian et al., 2019).

The use of biometeorological indexes to assess the impacts of atmospheric conditions on human health is preferred to using typical meteorological variables, since organisms are exposed simultaneously to multiple atmospheric factors.

Biometeorological indexes are composed of more than one atmospheric factor and can explain the effect that different environmental variables, in their interaction, cause on health and well-being of people (Royé et al., 2018a). Moreover, the use of biometeorological indexes is recommended by both the World Meteorological Organization and the World Health Organization to evaluate the impacts of heat stress on human health (Wong et al., 2017).

For instance, Apparent Temperature (AT) is a biometeorological index that can be used to estimate how the human body reacts to the set of conditions of the thermal environment. AT combines temperature, humidity and wind speed and is able to represent human thermal comfort. Under heat stress situations, the body uses four mechanisms of heat exchange to maintain homeostasis: conduction, convection, radiation, and evaporation; the evaporation process is affected by humidity conditions while the wind is determinant in the convection. Some authors consider AT to be the most important predictor of heat-related mortality (Steadman, 1984a; Royé et al., 2018b).

This study aims to describe temporal patterns in ischemic stroke (IS) in the Community of Madrid, Spain, between 2001 and 2013, and to analyze the relationship between ischemic stroke (admissions and deaths) incidence and AT and atmospheric pollutants on a daily scale. Furthermore, potential gender and age-group (over vs. under 64 years old) risk differences were also examined.

2. Methods

2.1. Study area

The Community of Madrid is an autonomous community of Spain located in the center of the Iberian Peninsula. Its capital is the City of Madrid, which is also the capital of the country. The region of Madrid has a Mediterranean climate with continental influences, characterized by hot summers and cool winters. Madrid's levels of industry set it at fourth place in Spain, and the star-shaped design of the Spanish road network makes it the central transport hub of the country. This, combined with a high amount of registered vehicles (4.221.800 in 2013) in the region, results in a heavy-traffic-supporting metropolitan area that suffers severe road congestion issues. Thus, road traffic is widely recognized as the main source of air pollution in Madrid (Laña et al., 2016), in which indoor air pollutants and the geographical characteristics of the region also play a relevant role.

Despite general downward trends in emissions over recent years (Querol et al., 2014), this region still presents exceedances of air quality legal limits according to the Directive 2008/50/EC.

2.2. Data sources

2.2.1. Health and demographic data

2.2.1.1. Hospital admissions. Data concerning admissions due to IS in the Community of Madrid, from January 1, 2001, to December 31, 2013, as categorized with ICD-9 (International Classification of Diseases, 9th Revision) codes 433 (Occlusion and stenosis of precerebral arteries), 434 (Occlusion of cerebral arteries) and 435 (Transient cerebral ischemia) were collected, including the date and length of admission and the patient's sex and age, from the *Encuesta de Morbilidad Hospitalaria* (Hospital morbidity survey) of the Spanish National Institute of Statistics (INE) database.

2.2.1.2. Mortality data. Mortality data obtained from the INE, for years 2001–2013 (incl.), were categorized according to the International Classification of Diseases (ICD-10), 10th Revision. We focused on mortality cases caused by cerebral infarction (I63) and strokes not specified as hemorrhage or infarction (I64). These cases were divided by the INE into three major age groups (15–44 years old, 45–64 years old and 65 years old or older), excluding deaths of children under the age of 15.

2.2.1.3. Influenza data. The weekly influenza rates in Madrid were obtained from the *Dirección General de Salud Pública* of Madrid's notifiable disease register (not laboratory-confirmed), and were used as an indicator of epidemics, representing a possible confounding variable (Ye et al., 2012a; Thach et al., 2010; Barnett et al., 2017).

The clinical surveillance of influenza is based on reports made by sentinel general practitioners. The sentinel surveillance system in Madrid reports weekly data on the number of new cases. A new case is defined as a sudden onset (<12 h) of at least one general symptom (fever, malaise, headache and/or myalgia) and at least one respiratory symptom (cough, sore throat and/or dyspnea) in the absence of another diagnostic suspicion.

The data are analyzed according to the population assigned to each sentinel doctor and the number of days of the week that the doctor attended to patients.

Moreover, from 2009, an automatic collection of influenza cases from the electronic clinical record of Primary Care has been performed.

2.2.1.4. Demographic data. To analyze incidence, annual population data of the Community of Madrid by sex and age groups were obtained, also from the INE. The average annual population during the study period in the Community of Madrid was 5,236,083 (2,516,930 men and 2,719,152 women).

2.2.2. Environmental factors

2.2.2.1. Air pollutants. We collected data of the main air pollutants (nitrogen dioxide in μg/m^3 [NO_2], ozone in μg/m^3 [O_3], sulfur dioxide in μg/m^3 [SO_2] and particulate matter with a diameter below 10 μm in μg/m^3 [PM_{10}]) for years 2001–2013 inclusive having almost complete datasets (2% missing values).

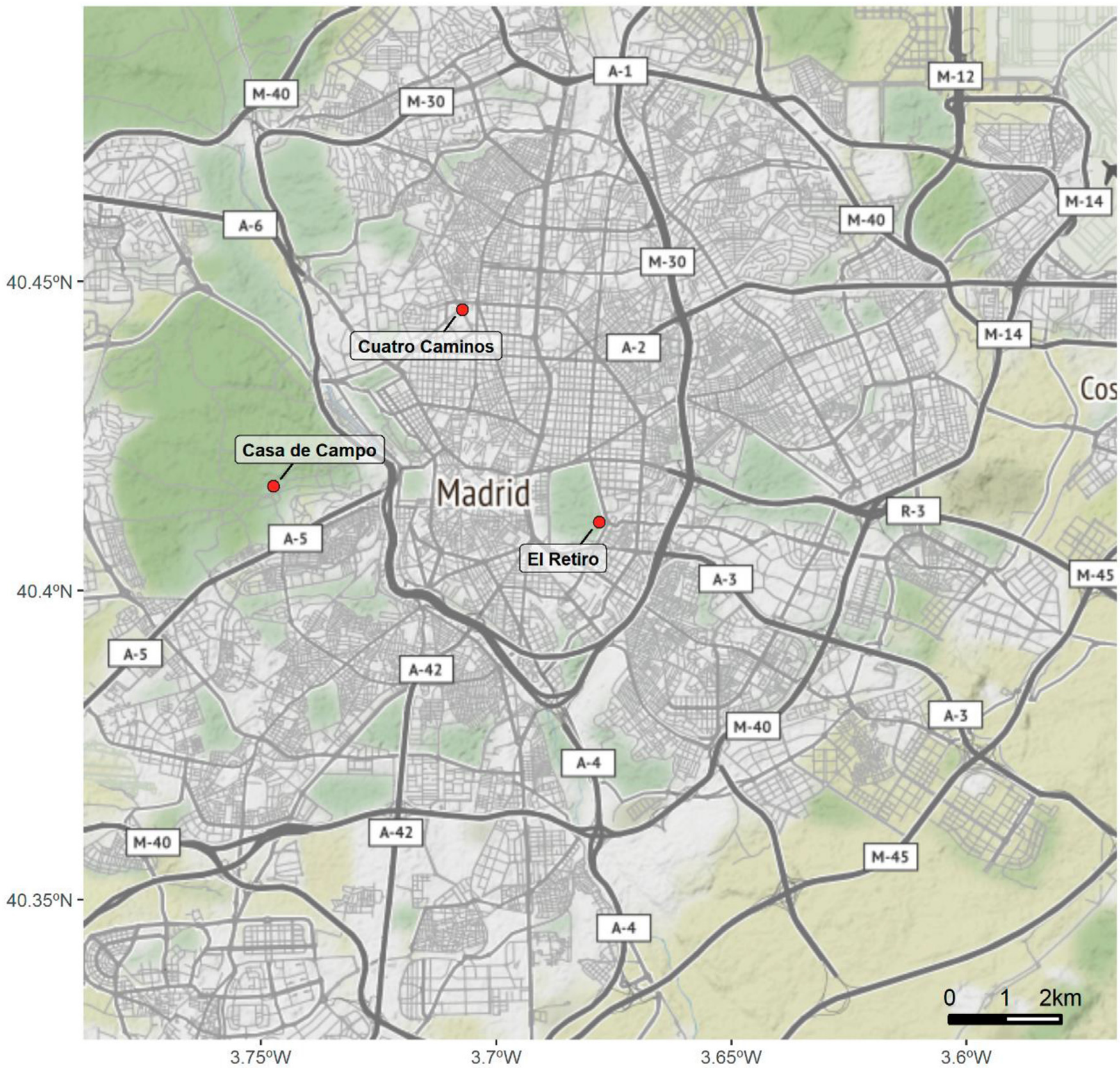
Series were obtained from two fixed monitoring stations: one of them (Casa de Campo) is classified as suburban and is located in the vicinity of the largest public park in the city of Madrid and was chosen due to having very few gaps in its temporal series; the second one (Cuatro Caminos) is a traffic station located in the city center, and was chosen as a control station in order to gauge whether our results were dependent on the location of the measurements (Map 1). Data were obtained from the "Red de Vigilancia de la Calidad del Aire" (Air quality monitoring network) of the Ayuntamiento de Madrid (Madrid City Council).

2.2.2.2. Apparent Temperature. The meteorological data were obtained from the European Climate Assessment and Dataset (ECA, http://eca.knmi.nl/) (Klein Tank et al., 2002). Daily average air temperatures (°C), relative humidity (%), and wind speed (m/s), obtained from the weather station known as "Madrid-El Retiro" (source identifier 230) with blended data for the period 2001–2013, were used. "Blended data" refers to observations of two nearby locations (within a distance of 12.5 km and with height differences of less than 25 m), which can be merged seamlessly for climate change research; in our case, less than 0.1% were replaced by data from nearby stations.

The daily AT was estimated for shade according to Steadman (1984b)

$$AT = -2.7 + 1.047 \cdot T + 2.0 \cdot P_v - 0.65 \cdot v_{10}\,. \tag{1}$$

where T is the temperature (°C), P_v is the vapor pressure (hPa), and v_{10} is the wind speed 10 m above the ground. P_v can be estimated with Equation (2):



Map 1. Location of the two air fix monitoring stations, Casa de Campo (suburban station) and Cuatro Caminos (traffic station), and of the weather monitoring station "El Retiro" in the Community of Madrid.

$$P_v = (rh/100)\cdot 6.1094\cdot e^{(17.625\cdot T)/(243.04+T)} \quad (2)$$

where *rh* is the relative humidity expressed as a percentage (Alduchov and Eskridge, 1996).

2.3. Statistical analysis

2.3.1. Incidence, seasonality and temporal trend

The annual incidence tendency was calculated by using the Kendall rank correlation coefficient. Specifically, the distribution of death rates by age group was analyzed. In order to compare the monthly average number of admissions, we employed an ANOVA F test. Additionally, post hoc t tests (Bonferroni corrected) were conducted for each pair of months separately.

2.3.2. Analysis of the relationship between environmental factors and stroke

The nonlinear relationship between the exposure and response variables was modeled using a distributed lag nonlinear model (DLNM). The DLNM framework simultaneously describes complex nonlinear and delayed effects of an environmental variable on a response variable with a family distribution and link function within generalized linear models (GLM), generalized additive models (GAM), or generalized estimating equations (GEE) (Gasparrini, 2011a, 2014a).

The possible lagged response on human health is a well-known phenomenon and expresses the temporal change in risk after a specific exposure event. To model the effects of IS for this study, a quasi-Poisson regression with GAM was fitted (Hastie and Tibshirani, 1990; Wood, 2006).

We assumed a non-lineal relationship for the temperature exposure and a lineal relationship for the contaminants.

Firstly, to analyze the relationship between AT and IS (controlling the pollution through PM_{10}) the following model was used:

$$Y_t \sim Quasi-Poisson(\mu_t)$$

$$Log(\mu_t) = \alpha + \beta_1 Eat_{t,l} + \beta_2 Epm10_{t,l} + s(Flu,\, 3) + s(Trend,\, 7\cdot 13) + \eta dow_t$$

Secondly, the relationship between individual pollutants and IS was studied by using the following model:

$$Y_t \sim Quasi-Poisson(\mu_t)$$

$$Log(\mu_t) = \alpha + \beta_1 Eat_{t,l} + \beta_2 Ec_{t,l} + s(Flu,\, 3) + s(Trend,\, 7\cdot 13) + \eta dow_t$$

where t is the day of the observation, Y_t is the daily mortality or morbidity rate for IS observed on day t, α is the intercept, $Eat_{t,l}$, $Epm10_{t,l}$ and $Ec_{t,l}$ are matrices obtained by applying the DLNM to AT, PM_{10} and single contaminants (NO_2, PM_{10}, SO_2, O_3), β is the vector of coefficients for each matrix and l is the lagged effect in days. s(…) is a thin plate

regression spline. *Trend* is the long-term trend and seasonality with 7 degrees of freedom (df) each year. *Flu* represents the daily smoothed number of reported influenza cases. dow_t is the day of the week on day t, and η is the vector of coefficient. Sunday is used as the reference day. Three df were used to smooth daily influenza rates considered to be potential confounders.

As far as the influenza rate is concerned, a polynomial local regression function (LOESS) (Cleveland et al., 1992) was applied to extrapolate the weekly data and thus obtain approximate daily records. A 14-day smooth window was chosen, which corresponds to smoothed behavior close to the declared cases (Iñiguez et al., 2001; Touloumi et al., 2005).

The selection of the degrees of freedom was made by using the Akaike Information Criterion. To model the nonlinear and lagged AT effects, a cubic B-spline with 3 df was used. For the lagged effects of each contaminants also a cubic B-spline with 3 df was applied.

While it is widely known that the effects of heat on morbi-mortality are quasi-direct with a delay of a few days (Ye et al., 2012b), the effects of cold can be delayed by up to 2 weeks (Gasparrini et al., 2015). Hence, a maximum lag of 14 days was used to model the effects of the exposure variables. As a reference value to calculate the relative risks in the case of the AT exposure variable, the threshold of minimum mortality and morbidity was estimated with the method applied by Tobías et al. (Bhaskaran et al., 2013).

A specific explanation of the statistical details regarding the distributed lag nonlinear model can be found in Bhaskaran et al. (2013) or Gasparrini (2014b).

In order to determine the possible differences between apparent temperature and air temperature, a sensitivity analysis was conducted. Finally, the sensitivity of using single and multi-air pollutant models was also evaluated.

All models, statistical analysis, and graphic results were made with the free software environment R, version 3.5. The models used in this study have been estimated through packages mgcv, version 1.8–23 (Wood, 1007), and dlnm, version 2.3.4 (Gasparrini, 2011b).

3. Results

3.1. Ischemic stroke hospital admissions

During the 13 years study period, there were 106,036 IS hospital admissions (including Transient cerebral ischemia). The average incidence rate was 133.5 cases per 100,000 population (142.8 per 100,000 population in male patients and 124.8 per 100,000 population in female patients). The average length of stay (ALOS) for each admission was 10 days (9.3 in men and 10.3 in women), decreasing every year from 11.8 days in 2001 to 8.3 in 2013 ($p = 0.000019$). The ALOS depending on the type of stroke and age-group is shown in Table S1.

The secular analysis showed an upward trend in the incidence rate of hospital admissions during the period of study that was statistically significant for the 3 defined age groups ($p < 0.005$), Fig. 1.

The monthly analysis showed that the number of hospital admissions due to IS followed a seasonal pattern reaching minimum values in August ($p < 0.005$, Bonferroni corrected), Fig. 2.

3.2. Ischemic stroke deaths

Between 2001 and 2013 there were 18,095 deaths by stroke (not including hemorrhagic strokes, but considering those which had not been specified as hemorrhage or infarction). The incidence rate followed a downward trend during the 13 years of analysis in the 3 age-group studied ($p < 0.005$). According to Fig. 2, the largest decline in mortality rate was observed for people older than 64 years old, reaching a maximum of 221.8 deaths per 100,000 population in 2001 and a minimum of 95 deaths per 100,000 population in 2013.

While the ANOVA model showed differences between months ($p < 0.005$) when analyzing annual patterns, by applying the Bonferroni correction, statistical significance was not found ($p > 0.05$).

3.3. Association between atmospheric variables and ischemic stroke

Table 1 shows descriptive statistics for meteorological and pollution variables. The wider range of apparent temperatures, compared with the air temperature, can be understood as the result of including wind speed and humidity to correctly describe the perceived thermal environment. The average AT for Madrid is 14.1 °C, reaching a maximum of 33.2 °C. Fig. 3 shows heatmap plots of daily morbi-mortality cases for IS according to lag and average AT in Madrid. The estimated associations for AT and IS were nonlinear, with clear associations at high temperatures which persisted, in a decreasing manner, up to a lag of 3–4 days. Longer lagged effects could be observed for low temperature ranges between 3 and 10 days. Furthermore, the behavior of lagged effects between IS mortality and morbidity is very contrary. In the latter case, an absence of effects in high temperatures and a lagged effect in low temperatures was found. The minimum mortality and morbidity were estimated at 11.7 °C (95% CI, 8.3–16.5) and 33.1 °C (95% CI, (−5.7-33.1) for the average AT, respectively. The maximum effect in IS hospital admissions was estimated at a low AT with a lag of 5 days. In Fig. 4, the cumulative effects for lag 0–14 days are represented for both response variables. With an AT of 1.7 °C (percentile 5%) a RR of 1.20 (95% CI, 1.05–1.37) for IS mortality and a RR of 1.09 (95% CI, 0.91–1.29) for morbidity is estimated (Tab 2). Although the overall risks are not significant for stroke hospital admissions, a RR of 1.02 (95% CI, 1.00–1.04) at lag 5 with −1.5 °C AT could be found. In the case of IS mortality the maximum risk at low AT is reached at lag 6, with 1.7 °C a RR of 1.03 (95% CI, 1.01–1.04) was estimated (see Table 2).

Higher risks were observed for high temperatures, particularly in stroke mortality, with an estimated RR of 1.37 (95% CI, 1.07–1.75) at 26.2 °C (percentile 90%).

In Fig. 5, the comparison between the use of apparent and air temperature as an exposure variable for the cumulative effects is presented. It shows clearly that the RR decreases when using AT, particularly in the case of low temperatures.

Regarding gender differences, men show higher risks of mortality in low temperatures and women in high temperatures (Fig. 6), although only significant effects are observed in percentiles 1% for men and over 90% for women. At 27.9 °C of apparent temperature (percentile 95%) the RR of mortality is 1.06 (95% CI, 0.97–1.15) in men and 1.17 (95% CI, 1.09–1.26) in women at the same day of exposure. In the case of a low temperature of 1.7 °C a risk of 1.03 (95% CI, 1.01–1.06) in men and 1.00 (95% CI, 0.97–1.03) in women for a lag of 7 days is observed. IS hospital admissions also show a non-significant higher risk for low temperature in men than in women (Table S2, Fig. S1) (see Table 3).

When estimating the effects of the AT only for those older than 64 years, the risks of mortality due to cold effects decreases. For instance, the RR for 1.7 °C AT is 1.13 (1.00–1.27), compared to the risk of all ages with 1.20 (95% CI, 1.05–1.37) (Table 4, Fig. S2). It is necessary to emphasize the fact that only 3% of IS mortality is population with less than 64 years. On the contrary, this proportion rises to 21% in IS hospital admissions. People younger than 64 seem to have higher risk for low temperatures, but these effects are not significant. In the case of IS hospital admissions, the risk estimates for 64-year-old group are very similar but become significant.

The results for individual pollutants showed inconsistency and are non-significant in the risk estimation for IS morbi-mortality (Table 5). The maximum effect in IS mortality was observed for each increase of 10 μg/m^3 SO_2 with a RR of 1.09 (95% CI, 0.90–1.31). In the case of NO_2 and PM_{10} the RR were 1.01 (95% CI, 0.99–1.04) and 1.02 (95% CI, 0.99–1.05) for each increase of 10 μg/m^3, respectively. In contrast, for IS hospital admissions, only O_3 showed an increasing risk with an RR of

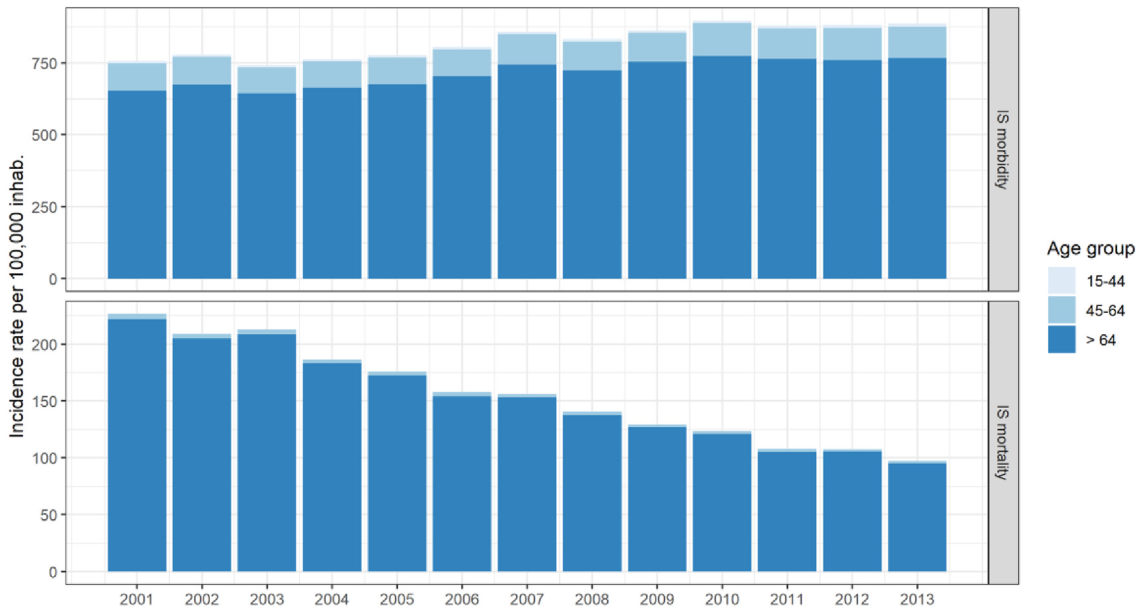


Fig. 1. Tendency of admission and mortality annual rates of patients suffering from Ischemic Stroke during a 13-year period (2001–2013) by age group in the Spanish province of Madrid.

1.01 (95% CI, 0.99–1.02) (per 10 μg/m^3). The sensitive analysis for two or more pollutant models showed that, in general terms, the risk estimates decrease with more contaminants and the effects continue to be non-significant. The risk of mortality for NO_2 and SO_2 showed higher risks for men than for women (Tab S3), although these effects are not significant. Women seem to have higher risks for PM_{10}. We did not observe any gender differences in IS hospital admissions. Finally, for the analyzed age groups we did not find differences for pollutants risk estimates in IS morbi-mortality.

4. Discussion

Over the last decade, the environment, including air pollutants, is gaining more and more importance in the pathogenesis of neurodegenerative disease but also other neurological conditions such as stroke, by either direct or indirect mechanisms that may involve epigenetic changes (Dimakakou et al., 2018; Riancho et al., 2018; McArthur et al., 2010).

The present study was conceived to elucidate several issues. First, we assessed the tendency and annual cycle of admission and mortality rates of patients suffering from IS during a 13-year period in the Spanish province of Madrid. Then, based on the previous literature, we aimed to study if an association existed between IS admissions and mortality rates and the main atmospheric pollutants. Finally, we investigated the relationship between AT and IS.

Regarding the first point, admission rates progressively increased over the studied period, while the average length of stay decreased. These results are in line with other studies in the literature and might be explained both by: i) more aggressive and interventional policies of stroke management and ii) a better identification of stroke in Emergency Departments. Conversely, mortality rate tendencies exhibited a decreasing pattern, which was particularly marked among the oldest patients. The progressive implementation of stroke units entailing more rapid and successful revascularization therapies, as well as a more integrated care of patients suffering from stroke in these units appear to be crucial conditions explaining these facts. Moreover, modifiable risk factors which increase mortality rates among patients who suffered an IS, such as physical inactivity, dyslipidemia, hypertension, diet or cigarette smoking, are well known, and programs to systematically identify and treat those in all patients at risk for stroke are gradually being developed (Meschia et al., 2014).

Subsequently, data analysis showed a seasonal pattern over the whole studied period, with the lowest incidence during summer time. These results are concordant with other published studies which also reported seasonal variations in stroke frequency in different countries (Oberg et al., 2000; Díaz et al., 2013; Ha et al., 2017). Although the

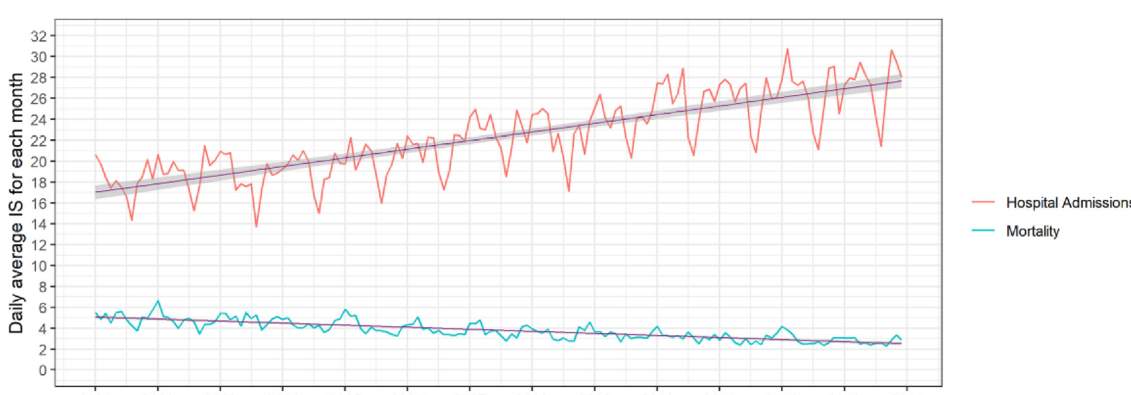


Fig. 2. Monthly calendar of Ischemic Stroke. Daily average of Ischemic Stroke admissions (red) and deaths (blue) for each month is represented. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Main characteristics of daily atmospheric and pollution variables during the study period 2001–2013.

	Relative Humidity (%)	Air Temperature (°C)	Wind Speed (km/h)	Apparent Temperature (°C)	SO_2	NO_2	PM_{10}	O_3
Min	22	−1.8	0	−5.8	1	1	3	2
Q1	45	8.8	14	6.8	5	16	13	31
Median	58	14.4	19	13.1	7	28	21	52
Mean	59.7	15.3	20.8	14.1	6.8	31.2	24.2	50.5
Q3	74	22.2	25	21.7	9	42	31	69
Max	97	32.8	106	33.2	23	119	163	148

Table 2
Temperature effect estimates for different percentiles.

Percentile	AT	Overall RR 0–14 days (95% CI)	
		Mortality	Hospital Admissions
1	−1.5	*1.38 (1.13–1.68)*	1.11 (0.93–1.32)
5	1.7	*1.20 (1.05–1.37)*	1.09 (0.91–1.29)
10	3.3	*1.13 (1.02–1.26)*	1.08 (0.91–1.28)
90	26.2	*1.30 (1.05–1.61)*	1.01 (0.95–1.07)
95	27.9	*1.37 (1.07–1.75)*	1.01 (0.96–1.05)
99	30.2	*1.48 (1.11–1.98)*	1.00 (0.98–1.03)

precise mechanisms involved have not been fully elucidated yet, some biological explanations have been proposed. Among them, the vasoconstriction due to cold, increased cholesterol and triglyceride concentrations in winter (Gordon et al., 1998), variations in both fibrinogen levels and plasma viscosity (Stout and Crawford, 1991) as well as some microbiological variations such as seasonal patterns of influenza epidemics and respiratory infections (Grau et al., 2006) are some of the most relevant ones. Moreover, sociodemographic variables and the personal medical history of the patient may play a role in seasonal vulnerability. In a recent study published by Toyoda et al., significant seasonal variations in IS (with a peak in winter) were only found in patients older than 75 years, with moderate-to-severe initial neurological deficits or when limited to those with cardioembolic stroke. Nevertheless, further studies with integrated and complementary approaches will doubtlessly help to clarify this issue, presumably providing us with new preventive and therapeutic strategies.

The role of environmental variables in stroke is gaining attention during the past years. To date, several studies have reported an association between environmental variables and stroke incidence (e.g. Gunes et al., 2015; Lim et al., 2017; Tobías et al., 2017). In the case of air pollutants, different researchers have described a significant correlation between nitrogen dioxide, sulfur dioxide or particulate matter and cerebrovascular diseases (Zhong et al., 2018; Santurtún et al., 2017a; Vidale and Campana, 2018). Moreover, regarding the possible etiopathogenesis of this association, some authors have stated that a short-term exposure to air pollutants is specifically associated with

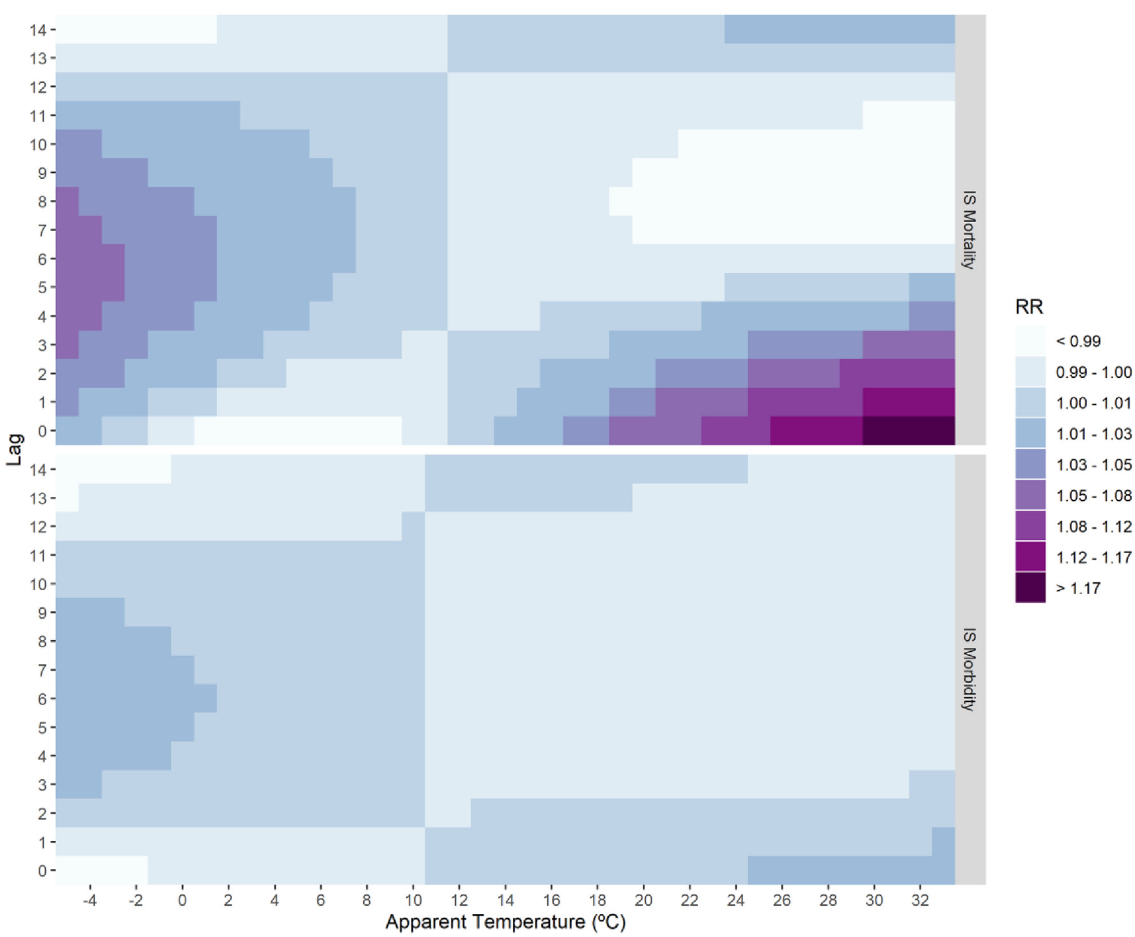


Fig. 3. Relative risk of daily Ischemic Stroke mortality and hospital admissions as a response to Apparent Temperature by lag period.

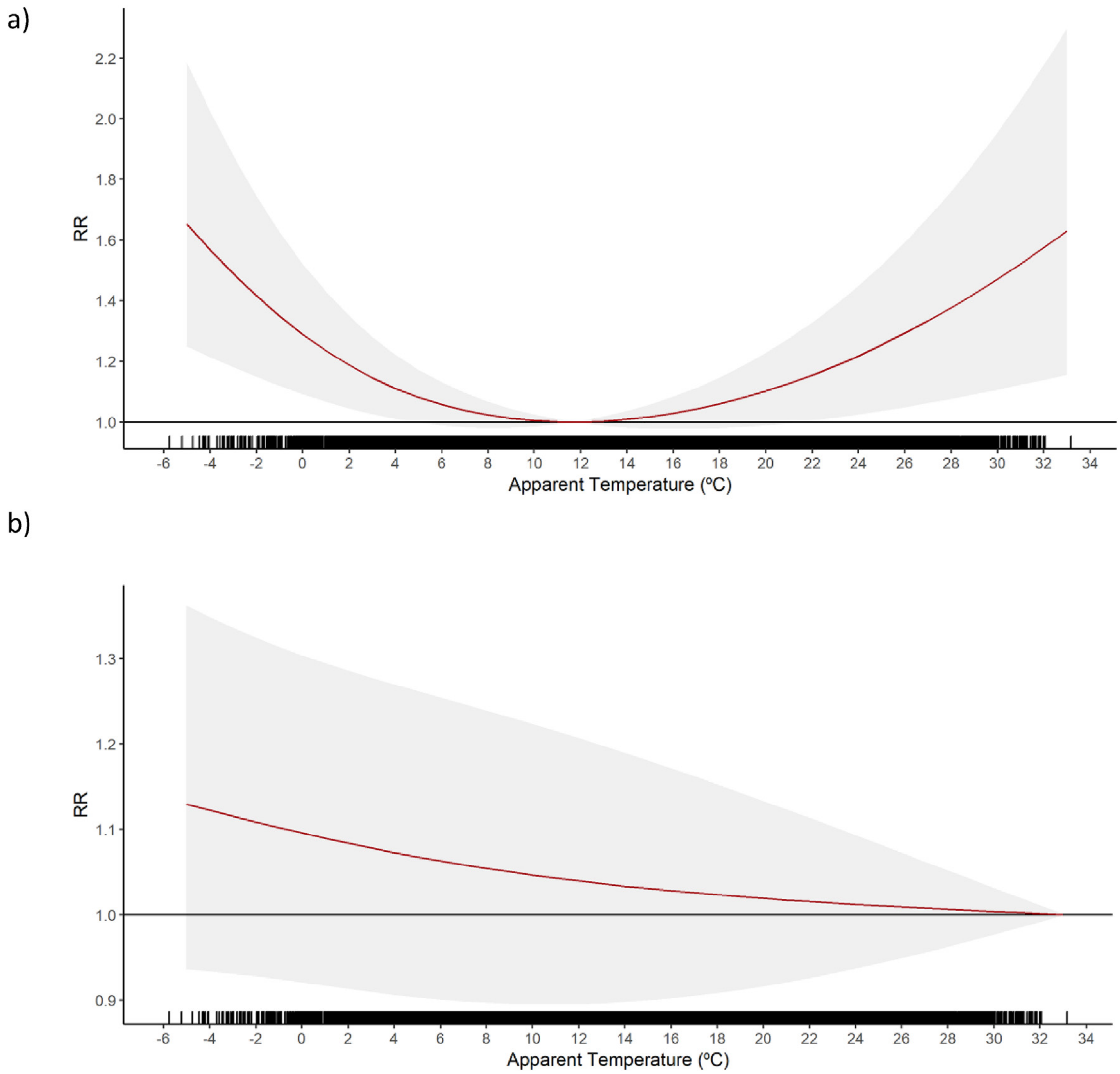


Fig. 4. Cumulative RR lag 0–14 of daily Ischemic Stroke mortality (a) and hospital admissions (b) as a response to Apparent Temperature.

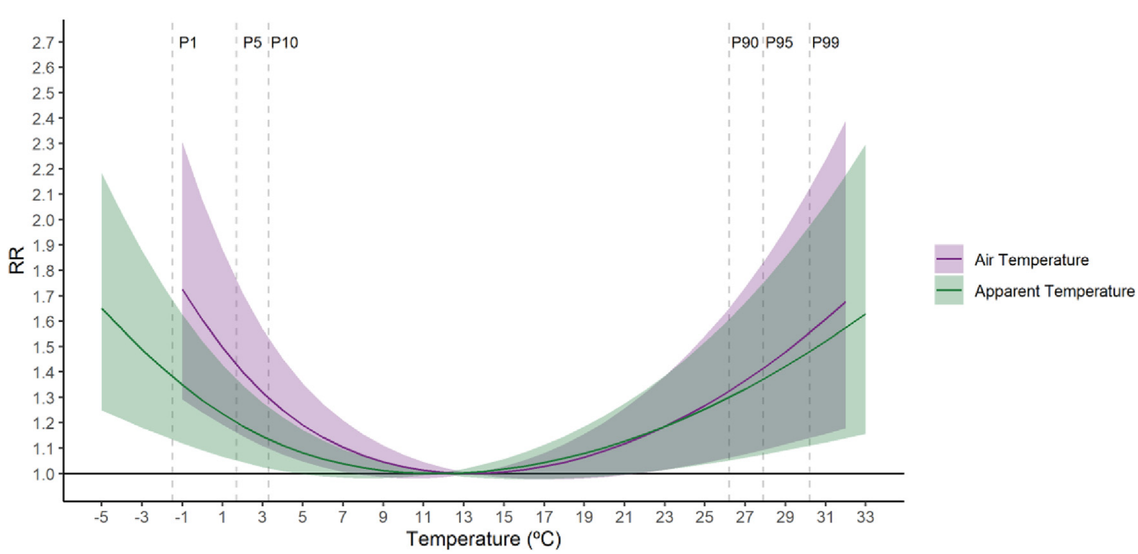


Fig. 5. Cumulative RR lag 0–14 of daily Ischemic Stroke mortality as a response to Apparent Temperature and air temperature.

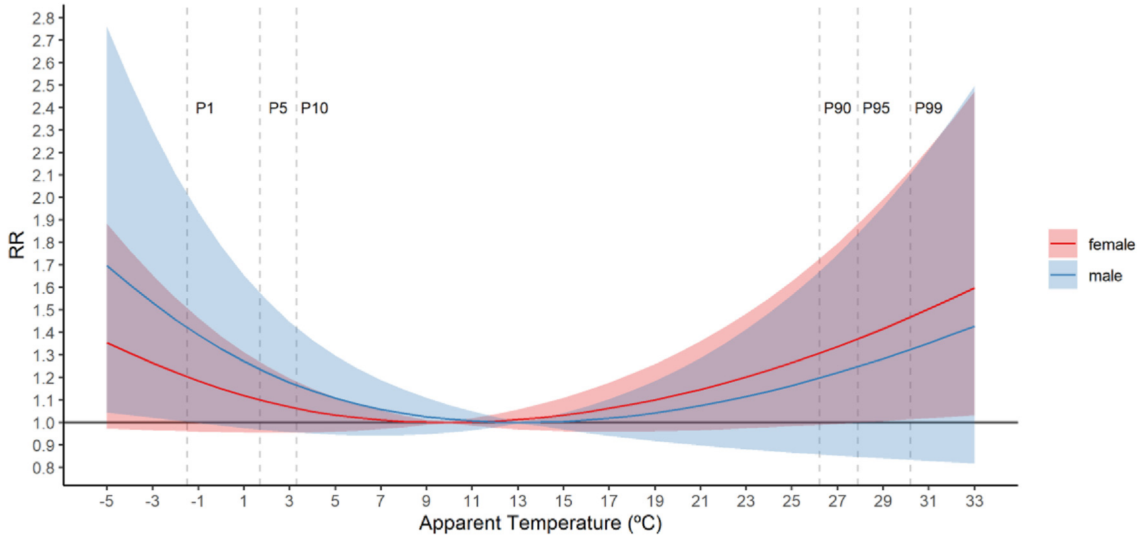


Fig. 6. Cumulative RR lag 0–14 of daily Ischemic Stroke mortality by gender as a response to Apparent Temperature.

Table 3
Temperature effect estimates by gender.

Percentile	AT	Overall RR 0–14 days (95% CI)	
		Male	Female
1	−1.5	*1.42 (1.00–2.02)*	1.20 (0.96–1.51)
5	1.7	1.23 (0.97–1.57)	1.10 (0.95–1.27)
10	3.3	1.17 (0.96–1.42)	1.06 (0.95–1.18)
90	26.1	1.19 (0.86–1.66)	1.30 (0.99–1.72)
95	27.9	1.25 (0.85–1.84)	*1.37 (1.00–1.88)*
99	30.3	1.33 (0.83–2.12)	*1.47 (1.01–2.14)*

Table 4
Temperature effect estimates by age group.

Percentile	AT	Overall RR 0–14 days (95% CI)	
		Older than 64 yr	Younger than 64 yr
1	−1.5	*1.25 (1.04–1.51)*	1.87 (0.67–5.22)
5	1.7	*1.13 (1.00–1.27)*	1.55 (0.80–3.01)
10	3.3	1.08 (0.99–1.19)	1.42 (0.85–2.36)
90	26.1	*1.30 (1.04–1.61)*	0.56 (0.17–1.89)
95	27.9	*1.37 (1.06–1.76)*	0.53 (0.13–2.15)
99	30.3	*1.47 (1.09–1.98)*	0.49 (0.09–2.57)

Table 5
Contaminant effect estimates (RR, 95% CI) for each increase of 10 μg/m^3.

Contaminants	Hospital Admissions	Mortality
PM_{10}	0,99 (0,97–1,00)	1,02 (0,99–1,05)
O_3	1,01 (0,99–1,02)	0,99 (0,96–1,02)
NO_2	0,99 (0,98–1,00)	1,01 (0,99–1,04)
SO_2	0,93 (0,85–1,01)	1,09 (0,90–1,31)

cardioembolic stroke (Chung et al., 2017), which would be in agreement with the relationship described between poor air quality and hospital admissions for cardiac arrhythmias in different places (Kowalska and Kocot, 2016; Santurtún et al., 2017b).

However, and in line with our results, other authors have not found these relationships (Crichton et al., 2016; Stockfelt et al., 2017). Nevertheless, the absence of a significant association with air pollutants should be understood with carefulness. The high pathogenic complexity of stroke should be considered when interpreting our results, since it can underrepresent the importance of these factors. Moreover, it is noteworthy that comparing results between different studies is not a trivial task, due to the fact that the area of study, the location and characteristics of air quality monitoring stations, the case registration systems, the adjustment for confounding variables and methodological designs, among other factors, vary greatly from work to work. Additionally, we would like to highlight that there are evidences which link chronic air pollution exposure with stroke and with reduced survival after stroke, a factor that is not considered in our study (Maheswaran, 2016).

Considering that climate change increases the risk of extreme events like heat waves and that the Intergovernmental Panel on Climate Change predicts an average global temperature increase in the range of 1.0 °C–6.4 °C until 2100 (Moghadamnia et al., 2018), the impact of air temperature is a concern for public health and is currently being thoroughly studied. Specifically, the role of this variable in stroke seems to be widely accepted. Recently, some authors have developed statistical models in order to infer years of life lost from stroke due to temperature variations in China (Li et al., 2018).

However, there has been little research on how AT affects human health. This biometeorological index combines several meteorological factors to describe the actual human perception of air temperature in a given environment (Royé et al., 2018a).

In this study we describe a significantly increased stroke-related mortality risk under extreme AT values (both low and high), with a maximum at the highest temperatures.

Although some potential biological mechanisms have been previously shown to explain the seasonal cycle of IS, at this point it must be noted that, besides the factors for IS described above, extreme temperatures have been demonstrated to cause platelet increase, hemoconcentration and the impairment of peripheral vascular endothelial function (Lian et al., 2015).

It is important to highlight that we found a higher RR when analysing the daily average air temperature than in the case of apparent temperature. It seems that the air temperature alone overestimates the potential risks and the combination of air temperature, humidity and wind speed adjusts the exposure to the thermal environment better. In general, the effect of temperature on relative humidity shows daily and seasonal cycles, with lowest relative humidity at high temperature and, conversely, highest relative humidity at low temperature.

It must be taken into account that, while different studies found a strong relationship between air temperature or wind speed with IS (Kim et al., 2016) and most authors describe no association between humidity and IS (Cao et al., 2016), the effects of the interaction between the different variables with the human body has not been thoroughly

studied. Humans use perspiration (sweating) to regulate internal body temperature, and high humidity impairs heat exchange efficiency by reducing the rate of moisture evaporation from skin surfaces. Meanwhile, in windy conditions, the convective rate is enhanced (Vanos et al., 2019). Moreover, from a statistical perspective, combining several variables is advisable to avoid and reduce multicollinearity in the model.

The lag structure found for AT with short-term IS mortality of few days at high temperatures and longer lags of more than 4 days at low temperatures is consistent with previous studies (Chen et al., 2013; Lavados et al., 2018; Yang et al., 2016). This delayed effect may be due to the fact that the exposure to an extreme AT may trigger one of the mechanisms that can cause a cerebrovascular attack (e.g. a prothrombotic situation or an arrhythmia), which may result in stroke a short time later. On the other hand, in many occasions, stroke-related deaths occur not in the very acute period but few days later.

Regarding the differences found between genders, other authors have described a greater vulnerability of women to dying from heat due to vascular processes (Pyrgou and Santamouris, 2018; Achebak et al., 2018) which has mainly been attributed to physiological differences in thermal regulation between both sexes. It must be considered that women have lower body mass, higher percentage of fat but lower of muscle, and lower circulatory volume than men. In situations of heat stress, the adaptive response is usually more difficult for women, who tend to accumulate more blood peripherally than men, have a decreased sweating capacity, increase their heart rate to a greater extent, and present a higher risk of dehydration (Burse, 1979).

The higher vulnerability of men to die from stroke in cold situations is a novel result. Some previous studies have found a greater vulnerability to cold among men (although not specifically by studying stroke) but there are discordant results in this regard (Liu et al., 2015; Sartini et al., 2016). It should be noted that alcohol consumption, which is more prevalent in men, as well as the differences in the type of occupation (for instance, outdoor work, more common in men, is associated with a longer exposure to extreme thermal situations) could be uncontrolled risk factors.

In respect of the lower vulnerability to cold among older people (over 64 years old), it is necessary to ponder if this is a statistical limitation of the study, if the younger age group represents noise for the model, or if there are actually different responses to the thermal environment depending on the age group. Following the hypothesis posed above regarding differences by sex, there exists the possibility that in younger adults, in situations of extreme temperatures, the exposure is more persistent than in the elderly (e.g., work-related exposure), and therefore these effects arise.

When hospital admissions were studied, no effect was found under high temperatures while a lagged effect in low temperatures appeared. The characteristics in the response or the vulnerability to heat of some population groups could explain this finding; for example, heat exposure could trigger the release of inflammatory mediators, increase ventilation and exacerbate chronic obstructive pulmonary disease, which is highly prevalent in the elderly and can lead to death after a stroke (Bunker et al., 2016); also, cardiovascular adjustments to heat stress are attenuated in healthy elder individuals, which could contribute to the greater prevalence of heat-related deaths in them (Gagnon et al., 2015).

In conclusion, our findings suggest that both increases and decreases in AT had a marked relationship with IS deaths, while hospital admissions were only associated with low apparent temperatures. This leads us to believe that, although high AT does not influence the frequency of stroke it may have an impact in stroke survival.

No significant relationship was found between air pollutant concentrations and IS morbi-mortality, but this result must be interpreted with caution, since there are strong spatial fluctuations of the former between nearby geographical areas that make it difficult to perform correlation analyses to the latter.

Conflicts of interest

Dominic Royé, María T. Zarrabeitia, Javier Riancho and Ana Santurtún declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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Appendix A. Supplementary data

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